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REGIOCHEMICAL CONTROL IN THE DIELS ALDER REACTIONS OF SUBSTITUTED NAPHTHOQUINONES: ORIENTATIONAL MANIPULATION IN THE SYNTHESIS OF ANTHRAQUINONES.

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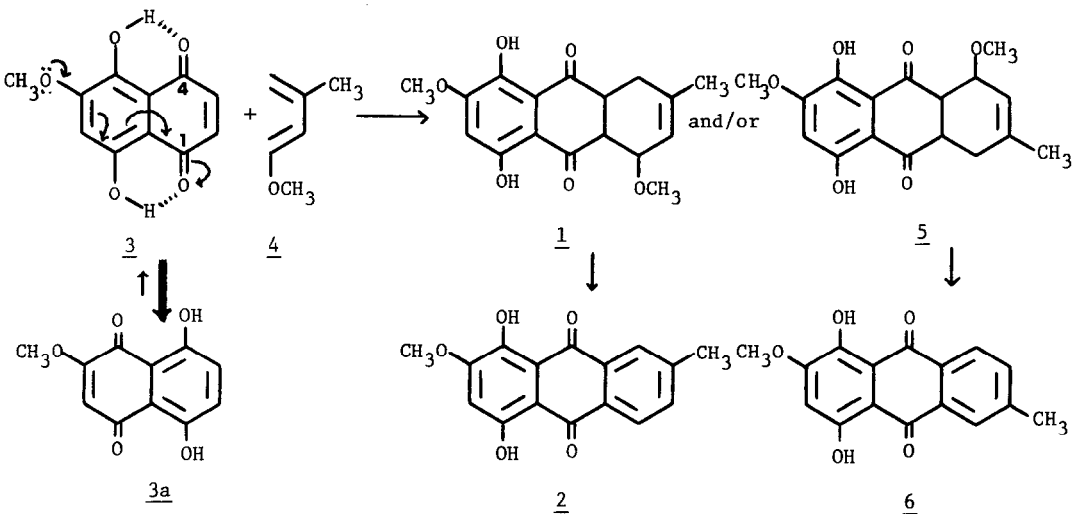
In conjunction with ongoing studies directed toward the development of a regiospecific synthesis of adriamycin, we recently advanced[1] a rationale for the regiochemical outcome of Diels Alder reactions between unsymmetric dienes and some oxygenated naphthoquinones. We now report the result of additional experiments which a) corroborate this hypothesis, b) illustrate its ability to predict regiochemical consequences and c) demonstrate how in a specific instance the constitution of an oxygenated naphthoquinone can be manipulated to obtain a desired regioisomer.

In the course of other work, it was desirable to devise a regiochemically controlled route to molecules possessing structures and substitution patterns such as those found in 1 and 2. Retrosynthetic analysis suggested that 1 might be readily available from the Diels

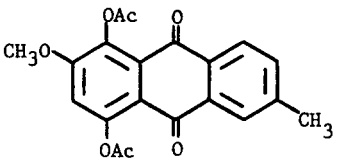


3 4 1 5

3a 2 6

Alder reaction between naphthopurpurin monomethyl ether (3)[2] and diene 4[3]. Further analysis suggested, however, that the cycloaddition of 3 and 4 might produce the undesired regiomer 5 preferentially, since, to a first approximation, the two hydrogen bonding interactions in 3 should cancel, and the C-4 carbonyl should therefore control the regiochemical outcome of the reaction because of the "deactivation" of the C-1 carbonyl by resonance donation from the methoxy group (3, arrows). In practice this predicted outcome indeed obtains. Thus, reaction of 3 with excess 4 at 95° (2 hrs, neat) produces 1 and 5 in approximately a 1:3 ratio.

Treatment of a THF solution of this crude mixture with aq KOH in the presence of air (½ hr, 25°) affords, upon workup and isolation, a ~1:3 ratio of 2 and 6 in ~75% overall yield. Fortuitous (and unreproducible) fractional recrystallization of the initial 1:3 mixture from ether provided the major isomer (6) in pure form (orange-red needles mp 235~239°), the structure of which was established by conversion (Ac_2O, pyridine, 25°) to 7, yellow needles, mp 192-7° after sublimation (170°/0.05 torr) and recrystallization from benzene. The nmr spectra of 7 and the known[4] 8 are virtually superimposable, but the two compounds



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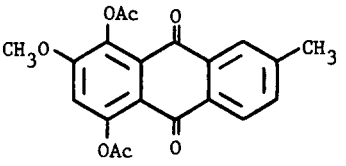

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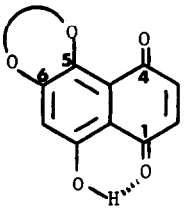

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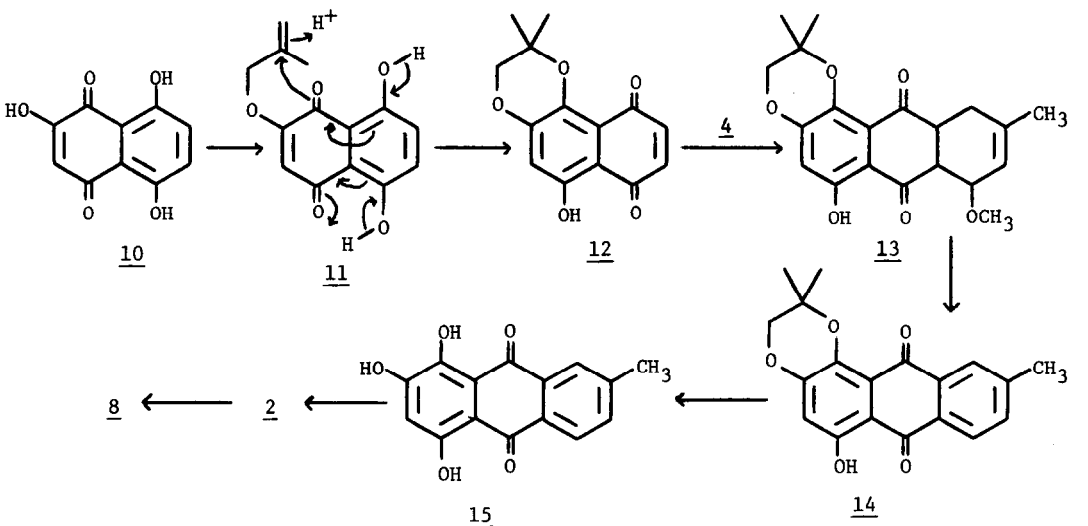
differ substantially in physical properties [8 (lit)[4]: prisms, mp 238-43°]. Consequently, the principal adduct of 3 and 4 must be 5*.

Having established that the predicted - but undesired - regioisomer (5) predominates in the reaction between 3 and 4, a means for reversing the regiochemical outcome of the Diels-Alder reaction was required. Further consideration suggested that replacement of 3 with a molecule of the generalized structure 9 might lead to the desired regiochemical outcome since the resonance donation properties of the C-5 and C-6 oxygens should approximately cancel, thereby allowing the C-1 carbonyl to determine the regiochemical outcome due to its "activation" by hydrogen bonding with the peri-hydroxyl group. This expectation was borne out (Scheme 1)



Scheme 1

* The possibility that 7 might be a different crystalline form of 8 is excluded by the fact that 8 was subsequently prepared from 2, which is demonstrably different from 6 (see Table 1 and text).

Table 1: NMR Spectra (in $CDCl_3$, δ)

Compound	peri-OH Singlets	Other distinctive resonances
1	11.85, 12.70	1.80(3H,s); 3.00(3H,s); 3.90(3H,s), 6.64(1H,s)
2	13.38, 13.48	2.60(3H,s); 4.09(3H,s); 6.73(1H,s)
5	12.11, 12.49	1.80(3H,s); 3.00(3H,s); 3.90(3H,s); 6.62(1H,s)
6	13.42, 13.46	2.60(3H,s); 4.09(3H,s), 6.73(1H,s)
7	----	2.49(9H,s); 3.92(3H,s); 6.91(1H,s); 7.4-8.1(3H,m)
8	----	2.51(9H,s); 3.93(3H,s); 6.91(1H,s); 7.4-8.15(3H,m)
11	12.25, 12.68	1.83(3H,br s), 4.51(2H,s); 5.10(2H,br s), 6.10(1H,s); 7.20(2H,s)
12	12.79	1.41(6H,s); 4.03(2H,s); 6.72(1H,s); 6.77(2H,s)
13	12.60	1.32(3H,s); 1.44(3H,s); 1.81(3H,br s) 3.01(3H,s); 4.02(3H,s); 5.71(1H, br s); 6.63(1H,s)
14	13.40	1.46(6H,s); 2.48(3H,s); 4.07(2H,s)
15	13.25(2H,br s)	2.55(3H,s); 6.75(1H,s)

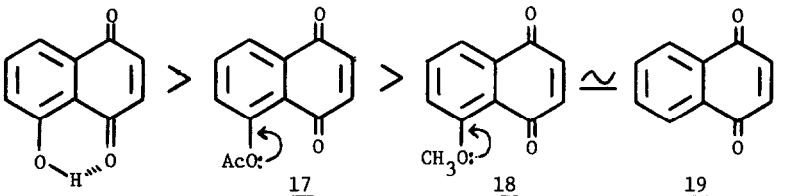
Alkylation of the most acidic[2] OH group of naphthopurpurin (10)[5] by treatment (~1hr) with Ag_2O in refluxing methallyl chloride gave 11 (mp 170-171.5 from EtOH) in yields occasionally exceeding 10%[6] after purification by tlc (SiO_2, CH_2Cl_2). Addition of conc. H_2SO_4[7] (3.5 cc) to a stirred solution of 11 (36 mg) in 1.8 cc $CDCl_3$ gave a purple mixture which after 5 min was poured over ice to give 12 in essentially quantitative yield (nearly black crystals from ether which char without melting at 130~150°).

Diels Alder reaction of 12 with excess 4 (2 hrs, 25°) gave 13 as apparently the only isomer formed (the position of the sharp singlet resonances of protons in hydroxyl groups peri to carbonyls is extremely sensitive to subtle molecular differences: see Table 1). The crude adduct (13) was converted directly (aq KOH, EtOH, air) to 14 (red orange crystals, mp 196-7° from ether) which, upon treatment with HBr/HOAc (100°, 18 hrs, sealed tube), afforded 15 [rust-colored crystals from ether, mp 232-4° (sinter at~195°)]. Selective methylation[8] of the unchelated hydroxyl group of 15 was achieved by brief (~1 min, 0°) exposure to excess diazomethane followed by quenching with excess acetic acid to give 2 in approximately 50% overall yield from 12 after plc (SiO_2, CH_2Cl_2); mp 237-9° from $CDCl_3$/TMS. The positions of the resonances of the phenolic protons of 2 (Table 1) differ distinctly from those of 6 and the presence of 6 could not be detected.[9] That the structure and regiochemistry assigned to 2 is correct was confirmed by conversion (Ac_2O, pyr, 3 hrs, 25°) to 8 (prisms from aq acetone, mp 242-48°, in agreement with literature[4] values cited above).

Thus, as predicted on the basis of general considerations, the use of 12 in place of 3 serves to reverse the regiochemical outcome of the Diels Alder reaction and affords the required regioisomer. These results lend strong support to our previously advanced[1] hypothesis of regiochemical control and illustrate the successful utilization and manipulation of the basic rationale to predict and achieve a desired outcome.

In conjunction with the work described above, the relative reactivity of a closely-related set of naphthoquinones toward 1-methoxy-1,3-cyclohexadiene has been determined using competition experiments (25° in $CDCl_3$, monitored by nmr). The results (below) are also in agreement with the rationale[1]. Thus 16 is the most reactive dienophile due to the activating, electron withdrawing effect of hydrogen bonding, while 18 is less reactive than 17 because the methoxy group is a stronger resonance donor (and, therefore, better deactivator) than

Relative Reactivity



16 17 18 19

the acetoxy group.[10] The seemingly anomalous observation that the reactivity of 19 is not intermediate between that of 16 and 17 can be explained on the basis of inductive withdrawal by the oxygen substituents. This inductive withdrawal should offset the deactivating effect of resonance donation and accounts for the reactivities observed relative to 19 (unlike resonance donation, inductive withdrawal, being more diffuse, should affect both carbonyls to a similar extent and therefore should have only minor effects on regiochemical outcome). The difference in the rates of reactivity of 16 and 19 is approximately one order of magnitude.

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References and Notes

1. T.R. Kelly, J.W. Gillard, R.N. Goerner, Jr. and J.M. Lyding, J. Am. Chem. Soc., 99, 5513 (1977).
2. C. Kuroda, Proc. Acad. Tokyo, 15, 226 (1939). Compound 3 exists primarily as the tautomer 3a [R.E. Moore and P.J. Scheuer, J. Org. Chem., 31, 3272 (1966)] but only Diels Alder adducts of tautomer 3, which is evidently in facile equilibrium with 3a, have been observed. For a related example see L.F. Fieser and J.T. Dunn, J. Am. Chem. Soc., 59, 1016 (1937).
3. Prepared in 49% yield from methacrolein and $\phi_3P{=}CHOCH_3$ in ether, b.p.(Kugelrohr): 48-50° (30 torr) . We thank Mr. Joseph Magee for preparing this material.
4. T. Noda, T. Take, T. Watanabe and J. Abe, Tetrahedron, 26, 1339 (1970). In the experimental section of this paper compound "VIII" (=8) is misnumbered as "VII" (T. Noda, personal communication).
5. Prepared from naphthazarin either by the method of Kuroda[2] or by (unpublished observations of Dr. M. Montury) hydrolysis of 2,5,8-triacetoxynaphthoquinone [J.F. Garden and R.H. Thomson, J. Chem. Soc., 2483 (1957)]. We thank Dr. Montury and Mr. Kevin Tracey for preparing this material and Mr. Richard Rogers for his assistance. Use of impure naphthazarin in either preparation is disastrous.
6. It is believed that the poor yield is due to competing oxidation by Ag_2O. Alternate routes to 11 remain to be explored.
7. Cf. R.H, Thomson, "Naturally Occurring Quinones", 2nd Ed., Academic Press, New York, 1971; p 206 and references therein.
8. Cf. A. Stoessl, Can. J. Chem., 47, 767 (1969).
9. Due to the closely similar chemical shifts of the phenol protons of 2 and 6, we cannot rigorously exclude the possibility that a small amount ($<15\%$) of 6 was present. However, the absence of "extra" resonances attributable to regioisomers in the nmr spectra of 13, 14 and 15 suggests that at a minimum formation of 13 is highly regioselective. Appropriate precautions were taken to ensure that inadvertent "loss" of a minor regioisomer did not occur in the conversion of 12 to 2.
10. C.G. Swain and E.C. Lupton, Jr., J. Am. Chem. Soc., 90, 4328 (1968).